PELLETS 4.0 – ADVANCED FLUIDIZED BED TECHNOLOGIES

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INTRODUCTION

Fluid bed processes were first developed for the chemical industry to achieve better drying efficiencies than obtained with existing technologies *e. g* with tray drying. Implementation of spray nozzles in the fluid bed equipment enabled granulation processes, resulting in porous agglomerates and, processed to tablets, facilitating fast dissolution. With the development of the bottom spray technology highly efficient coating and layering processes became possible. While in the beginning this technology was mainly used for tablet coating, more and more processes were developed for coating of smaller particles, *i. e.* multiparticulates like pellets, minitablets and powders (*e. g.* API crystals).

Multiparticulate dosage forms consist of small discrete units with particle sizes of 100 – 2000 µm [1] showing a matrix structure (API implemented in the core) or being API layered. In case of pellets or minitablets, functional coatings can be applied, resulting in taste masking, gastroresistant coatings or other specific release profiles. Filling of multiparticulates into capsules or sachets and administration via sprinkling on liquids or food makes them attractive for patients who are not able to swallow monolithic dosage forms, as is the case for children or elderly. The possibility of administering different amounts of multiparticulates provides an opportunity for the development of individualized medicines. Also a compression into tablets is possible, orally disintegrating tablets (ODTs) release their discrete units in the stomach, ensuring a controlled drug release and less dependency on the gastric emptying.

Glatt offers several batch-wise or continuous technologies for the production of multiparticulates, matrix or layered pellets. Process development and optimization can be performed with quality by design approaches, process monitoring and control by state of the art PAT tools. The presentation will give an overview about the recent and most prevalent manufacturing methods.

BATCH FLUID BED TECHNOLOGIES

WURSTER TECHNOLOGY

The Wurster technology [Figure 1] is a classic fluid bed technology used for drug layering and (functional) coating of even very small multiparticulates and powders. The layering or coating liquid is sprayed concurrently with the fluidization air into the circulating fluid bed. The liquid is frequently and repeatedly applied as droplets on the substrate [Figure 1] in an environment of high heat transfer, finally resulting in a dense coating.

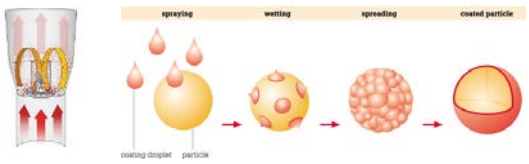

Figure 1: Wurster technology, coating process (Glatt Pharmaceutical Services GmbH & Co. KG)

CPS™ TECHNOLOGY

The CPS™ technology [Figure. 2] allows the preparation of both high drug loaded as well as low dosed matrix pellets, with sizes down to 150 µm. Based on advanced fluid bed rotor technology, the CPS™ technology works with a conical shaped rotating disc

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and devices providing a directed product flow. No starting beads are required. The powder, containing API and typically microcrystalline cellulose is wetted by the pelletizing liquid until a pre-defined moisture level (and with this: particle size) is obtained. Due to centrifugal forces, spherical particles are formed and densified, characterized by smooth surfaces, narrow particle size distribution [Figure 3] and low porosity and attrition.

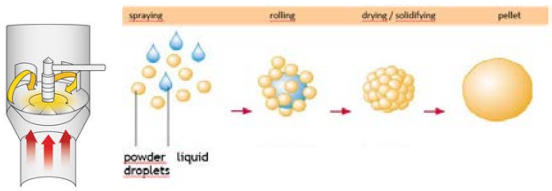

Figure 2: CPS™ technology, pelletizition process (Glatt Pharmaceutical Services GmbH & Co. KG)

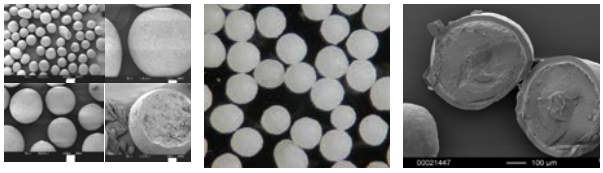

Figure 3: Matrix pellets produced with CPS™ technology (left), and MicroPx™ technology (middle, and right, Glatt Pharmaceutical Services GmbH & Co. KG)

CONTINUOUS FLUID BED TECHNOLOGIES

MICROPX™ / PROCELL TECHNOLOGY

The MicroPx™ technology is the preferred option for the production of high drug loaded pellets with API contents up to 95%. Spherical and smooth particles in the size of 150 µm or bigger can be obtained [Figure 3], exhibiting narrow particle size distributions. In this continuous process, the API containing liquid (solution, suspension, emulsion, melt [2]) is sprayed into the empty process chamber. Initially, fine powder is generated by spray drying, which is continuously agglomerated to seeds, and by further layering, to round pellets. Well-sized pellets are discharged by a sifter; the classifying air determines the resulting particle size. The process is characterized by a balanced ratio between spray drying, layering and discharging of well-sized pellets.

In contrast to the MicroPx™ technology the process gas enters the process chamber in the ProCell™ not through an inlet air distribution plate, but through slots in the lower part of the equipment, resulting in a spouted bed [Figure 4]. The contact of the product to hot surfaces is minimized, therefore this technology is applicable also for heat sensitive substances like enzymes.

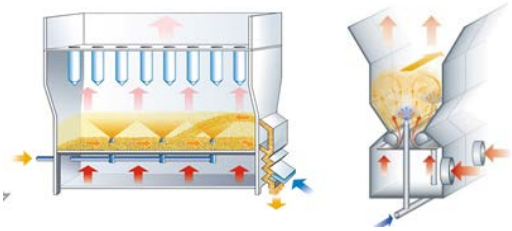

Figure 4: MicroPX™ (left) and Procell™ (right) technology, pelletization process (Glatt Pharmaceutical Services GmbH & Co. KG)

PROCESS CONTROL

For the implementation of robust and reproducible production processes, the critical quality attributes for a manufacturing process shall be known [3]. After a risk analysis, a design of experiments (DoE) with planned trials is applied, to define the design space and a control strategy for selected process parameters. PAT tools *e. g.* for online measurement of moisture, API content and particle size distribution can be applied for automated end point detection, to reduce the offline control and release testing.

SUBSCRIPT

API	Active pharmaceutical ingredient
DoE	Design of experiments
ODT	Oraly disintegrating tablet
PAT	Process analytical technology
QbD	Quality by Design

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[3] ICH Guideline, Pharmaceutical Development Q8 (R2) [2009]

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